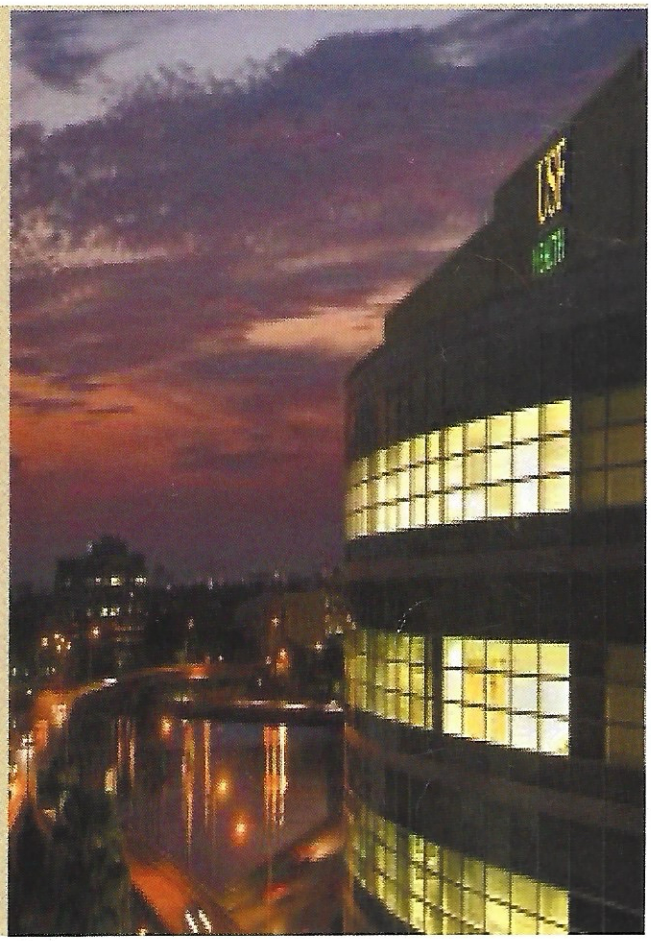
UNIVERSITY OF SOUTH FLORIDA

Division of Allergy and Immunology
Department of Internal Medicine
Joy McCann Culverhouse Airway Disease Research Center and The James A. Haley V.A. Medical Center
Tampa, Florida



2008-2009 Annual Report

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Visit our web page at:
http://hsc.usf.edu/medicine/internalmedicine/allergy/cru.html

USF HEALTH

Contents

University of South Florida College of Medicine, Department of Internal Medicine, Division of Allergy and Immunology

The late Samuel C. Bukantz, M.D., founded the University of South Florida College of Medicine, Department of Internal Medicine, Division of Allergy and Immunology in 1972. Richard F. Lockey, M.D. succeeded Dr. Bukantz in 1983 and is the current Director of the Division. Mrs. Joy McCann Culverhouse endowed the Division in 1997 and The Joy McCann Culverhouse Airway Disease Research Center was dedicated in February 1998. In 1998, Mabel and Ellsworth Simmons endowed the Division with a grant for education and research. The goals of the Division are: first, to provide care to patients with allergic and immunologic diseases at the University of South Florida College of Medicine, Tampa General Hospital, James A. Haley V.A. Medical Center, All Children's Hospital, and H. Lee Moffitt Cancer Center; second, to train students, residents, and fellows in the subspecialty of allergy and immunology; and third, to conduct basic and clinical research in allergy, asthma, and immunology.

Individuals interested in collaborating with members of the Medicine Division may contact Richard F. Lockey, M.D. or any faculty member at (813) 972-7631 (e-mail: rlockey@health.usf.edu). John W. Sleasman, M.D. or any other faculty member in the Pediatric Division may be contacted at 727-553-3533 or Jsleasma@health.usf.edu.

UNIVERSITY OF SOUTH FLORIDA

USF HEALTH

Dr. Richard Lockey named President of the World Allergy Organization

Richard F. Lockey, M.D.

Congress President, World Allergy Congress 2011

Richard F. Lockey, M.D., will serve as President of the World Allergy Organization (WAO) for the 2010 -2011 term. Elected to the WAO Board as member-at-large in 1998, Dr. Lockey served on the Executive Committee as Treasurer during the 2006-2007 term and President- Elect 2008-2009 term.

In addition to his position as President of the WAO , Dr.Lockey is a member of the American Academy of Allergy and Immunology (Fellow and Past-President, 1992-1993), the American College of Physicians (Fellow), the American Thoracic Society, Clinical Immunology Society, and the European Academy of Allergy and Clinical Immunology. Among his many achievements, he was recognized by his peers in 2007 for the honor of becoming a University of South Florida Distinguished University Health Professor.

The World Allergy Organization (WAO) is an international federation whose members consist of 84 regional and national allergy and clinical immunology societies from around the world. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to members in countries throughout the world. It also sponsors a World Allergy Congress every two years. Dr. Lockey will be Congress President for the World Allergy Congress to take place in Cancun, Mexico, from December 4th - 8th, 2011.

The organization was founded in 1951 and has successfully organized 20 major congresses. WAO also sponsors scientific symposia in developing areas throughout the world and jointly sponsors postgraduate programs on allergy and clinical immunology during professional, non-allergy or association congresses.

WAO is expanding its purview in a direct effort to bring together the member allergists and clinical immunologists who are engaged in research and/or clinical practice throughout the world. The organization provides advice and active support to member societies with the mission of building a global alliance of allergy societies which will advance excellence in clinical care, research, education and training in allergy / clinical immunology.

DIVISION OF ALLERGY AND IMMUNOLOGY
FACULTY AND STAFF

Core Faculty

Richard F. Lockey, M.D., University Distinguished Health Professor, Professor of Medicine, Pediatrics, and Public Health; Division Director; Joy McCann Culverhouse Chair of Allergy and Immunology

Roger W. Fox, M.D., Professor of Medicine, Pediatrics and Public Health

Dennis K. Ledford, M.D., Professor of Medicine and Pediatrics

Shyam S. Mohapatra, Ph.D., Mabel & Ellsworth Simmons Professor of Medicine, Director of Basic Research, Division of Allergy and Immunology-Joy McCann Culverhouse Airway Disease Research Center, Director, USF Nanomedicine Research Center.

Mark C. Glaum, M.D., Ph.D., Assistant Professor of Medicine and Pediatrics

Homero San-Juan-Vergara, M.D., Ph.D., Assistant Professor of Medicine

Narasaiah Kolliputi, Ph.D., Assistant Professor of Medicine

Srinivas Nagaraj, Ph.D., Assistant Professor of Medicine

Michael Teng, Ph.D., Assistant Professor of Medicine

Weidong Xu, Ph.D., Research Assistant Professor, Joy McCann Culverhouse Airway Disease Research Center

Arun Kumar, Ph.D., Research Instructor, Joy McCann Culverhouse Airway Disease Research Center

Weidong Zhang, M.D., Ph.D., Research Instructor, Joy McCann Culverhouse Airway Disease Research Center

Joint Faculty

John W. Sleasman, M.D., Professor of Pediatrics and Medicine; Robert A. Good Professor of Immunology; Chief, Division of Allergy and Immunology, Department of Pediatrics, University of South Florida, All Children's Hospital

Gary W. Litman, Ph.D., University Distinguished Health Professor, Andrew and Ann Hines Chair in Pediatrics, Professor of Pediatrics and Medicine

Stuart M. Brooks, M.D., Professor of Public Health and Medicine

Noorbibi Day, Ph.D., Professor of Pediatrics and Medicine

Sandra G. Gompf, M.D., Associate Professor of Medicine

My Lien Dao, Ph.D., Associate Professor of Biology and Medicine

Mitchel J. Seleznick, M.D., Associate Professor of Medicine

Mandel R. Sher, M.D., Associate Professor of Pediatrics and Medicine

Morna Dorsey, M.D., M.M.Sc., Assistant Professor of Pediatrics and Training Program Director, Pediatric Division

Subhra Mohapatra, Ph.D., Assistant Professor of Medicine

Robert Nickeson, Jr., M.D., Assistant Professor of Pediatrics and Medicine

Elena E. Perez, M.D., Ph.D., Assistant Professor of Pediatrics and Medicine

Michael Nieder, M.D., Affiliate Associate Professor of Pediatrics and Medicine; Director, Blood and Marrow Transplant Program, All Children's Hospital

Clinical Faculty

Robert E. Windom, M.D., Clinical Professor of Medicine

Monroe J. King, D.O., Clinical Associate Professor of Medicine and Pediatrics

G. Edward Stewart II, M.D., Clinical Associate Professor of Medicine

Hugh H. Windom, M.D., Clinical Associate Professor of Medicine

Rosa Codina, Ph.D., Clinical Assistant Professor of Medicine

Mary L. Jelks, M.D., Clinical Assistant Professor of Medicine

Brett E. Stanaland, M.D., Clinical Assistant Professor of Medicine

Nathan Tang, M.D., Clinical Assistant Professor of Pediatrics and Medicine

Glenn Whelan, Pharm.D., Assistant Professor of Medicine

Welcome to New Faculty Joining the Division in 2010

Narasaiah Kolliputi, Ph.D., Assistant Professor, joined the Division of Allergy and Immunology and the Nanomedicine Research Center at the College of Medicine. Dr. Kolliputi will develop translational strategies to attenuate acute lung injury (ALI) and ***acute respiratory distress syndrome*** (ARDS) using nanotechnology. Dr Kolliputi joins us from Massachusetts General Hospital, Harvard Medical School, where he was Research Scientist, studying the role of IL-6 signal transduction pathways and cell death in hyperoxic acute lung injury (HALI). Dr. Kolliputi received his postdoctoral training in the laboratory of Lung biology Laboratory at the Oklahoma State University, Stillwater, Oklahoma. Dr. Kolliputi is a graduate of Osmania University, Hyderabad, India, where he received a doctoral degree in Biochemistry with a focus in the area of signal transduction. His research interests focused on understanding the fundamental mechanisms that initiate and propagate the pathogenesis of ALI and to identify protective regulatory signaling mechanisms against ALI. Dr. Kolliputi is interested to start novel approaches in nanomedicine research to treat ALI/ARDS. He has authored and co-authored 10 peer reviewed publications. He has been recognized by the Society for Experimental Biology and Medicine, New Jersey and selected for Young Investigator Award 2009. Dr. Kolliputi obtained an independent National Scientist Development Grant from the American Heart Association.

Srinivas Nagaraj, Ph.D., Assistant Professor, at the USF Nanomedicine Research Center will be joining the Division of Allergy and Immunology in 2010. Dr. Nagaraj will help develop integrated technology to accelerate the translation of molecular and cellular knowledge into nanotechnology applications for medical and cell technologies. Dr. Nagaraj was previously a Research Assistant Professor in Immunology. Dr. Nagaraj earned his PhD from St. John's Medical College in Bangalore, India. He received his postdoctoral-training in Immune and Gene Therapy lab, Internal Medicine I, Uni-Clinic, Bonn, Germany and additionally trained in Immunology at Moffitt Cancer Center. His research interests focus on mechanism of tolerance in chronic inflammatory conditions and nanotherapeutic approach to differentiate suppressive populations. Dr. Nagaraj is enthusiastic to start new and exciting approaches in nanomedicine research. He has authored and coauthored over 25 journal articles and book chapters some of which have been included in Nature Medicine, Nature Reviews Immunology, Journal of Experimental Medicine .

Michael Teng, Ph.D., Assistant Professor, will be joining the Division of Allergy and Immunology and the USF Nanomedicine Research Center in 2010. He graduated from the Massachusetts Institute of Technology with a bachelor's degree in Life Sciences then obtained his Ph.D. in immunology from the University of Chicago. He trained as a postdoctoral fellow at The Scripps Research Institute in the laboratory of Dr. Michael Oldstone, then as a research fellow at the National Institute of Allergy and Infectious Diseases. Dr. Teng then took a faculty position in the Department of Biochemistry and Molecular Biology at the Pennsylvania State University. His research program focuses on the role of host-virus interactions in the pathogenesis of respiratory syncytial virus infection. In addition, he is interested in examining how viral factors can influence innate and adaptive immunity to viruses. Dr. Teng has authored 29 peer-reviewed manuscripts and has been funded by the National Institutes of Allergy and Infectious Diseases and the American Heart Association.

2008-2009 Fellows-in-Training

Dennis Kim, M.D., 2nd year fellow, Chief Fellow

Efren Rael, M.D., 2nd year fellow

Michel Alkhalil, M.D., 1st year fellow

Robert Pesek, M.D., 1st year fellow

Research Staff Members

Sandhya Boyapalle, Ph.D.

Gary B. Hellermann, Ph.D.

Xiaoyuan (Sonya) Kong, M.D.

Guoqing Liu, Ph.D.

Jia-Wang Wang, Ph.D.

Weidong Xu, Ph.D.

Students and Visiting Research Scholars

Yvonne Davis, B.Sc.

Sang-Joon Park, M.D.

Teriane Wong, B.Sc.

Xiaoqin Wang, B.Sc.

Administrative Personnel

Administrative Assistant to the Division Director
***Michelle Grandstaff-Singleton,** LPN, Clinical Research Administrator and Administrative Assistant to the Division Director*

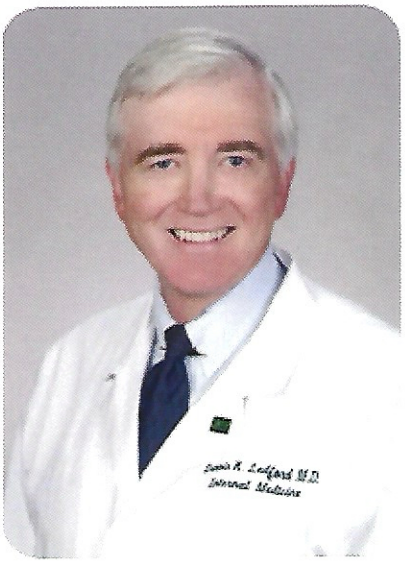
Administrative Personnel for the Division and The James A. Haley V.A. Medical Center
***Peggy Hales,** Program Assistant*
***Becci Carter,** Administrative Secretary*
***Geeta Gehi,** Administrative Secretary*

Administrative Personnel-USF Joy McCann Culverhouse Airway Disease Research Laboratory
***Mary Palmer,** Administrative Secretary*

Personnel for the Clinical Research Unit
***Michelle Grandstaff-Singleton,** LPN, Clinical Research Administrator*
***Shirley McCullough,** B.S., Clinical Research Coordinator*
***Diana Miller,** B.S., Clinical Research Coordinator*
***Sarah Lewis,** BFA, Regulatory Coordinator*

Administrative Personnel for All Children's Hospital
***Stacey Borst,** Training Program Coordinator*
***Amy Kramer,** Administrative Assistant to Dr. Sleasman*

Dr. Dennis Ledford
President-Elect of the American Academy of Allergy Asthma and Immunology in February, 2010



Dennis Ledford joined the faculty of the allergy/immunology division at the University of South Florida in 1984 after completing his fellowship in the specialty. He came to Tampa after studying at New York University and completing his residency in internal medicine at the University of Tennessee. He was promoted to professor of medicine and pediatrics in 2000. Dr. Ledford's contributions to the division have included clinical and basic research, contributions to the medical literature including serving as co-editor of the book Allergens and Allergen Immunotherapy and education of medical students and residents. He has been chosen as the outstanding teacher of the year by the USF medical house staff. He has served the University by completing two terms as Chair of the Medical Student Selection Committee and is a graduate of the inaugural Leadership Institute of USF. Dr. Ledford has served his community by supervising and staffing a clinic for subjects with asthma at the Judeo Christian Health Clinic and has received the outstanding medical volunteer of the year in Hillsborough County and the Governors Community Service Award from the American College of Chest Physicians. Dr. Ledford has served his specialty in a variety of ways including two terms as president of the Florida Allergy Asthma and Immunology Society, diplomat of the American Board of Allergy and Immunology and chaired the development of the maintenance of certification process for the board, Governor of the Regional State and Local Allergy Immunology Societies, board of director for the American Academy of Allergy Asthma and Immunology and will be the president-elect of this organization in February 2010. He is also active with the ACGME that oversees residency programs for allergy and immunology and currently serves as vice-chair.

BASIC RESEARCH PROJECTS

A. Inflammatory Lung Disease

1. The atrial natriuretic peptide (ANP) signaling pathway in pathogenesis of lung disease.

1a. Inhibiting ANP signaling through its receptor, NPRA reduces lung inflammation in an experimental asthma model.

The human body has many systems that do double duty. Kidneys filter impurities from the blood but also regulate the blood volume and levels of sodium and potassium. The heart pumps the blood but also makes hormones that regulate blood pressure. One of these heart hormones, ANP, plays an important role in regulating inflammation in the lungs. It activates several different kinds of cells by binding to a receptor called NPRA on the cell surface. Isatin is a small molecule drug that interferes with ANP signaling. Using an asthmatic mouse model, we have found that isatin inhibition of ANP signaling through NPRA reduces the inflammation in the lungs and allows the mice to breathe better. A derivative of the ANP prohormone, NP73-102, decreases the level of NPRA on the cell surface and inhibits ANP signaling. This year we have continued investigating the mechanism of NPRA action and developed new nanoparticle formulations to reduce inflammation and disease. The anti-inflammatory peptide, NP73-102, has proven to be a strong candidate for DNA-based therapy aimed at inflammation, cancer and virus infection. We are still working out how it acts but now have a clearer idea of the other proteins, such as Hsp-90, that it interacts with and this gives us a handle on understanding the mechanism.

1b. Other N-terminal natriuretic peptides are biologically active.

NP73-102 is not the only peptide derived from the ANP prohormone that has anti-inflammatory properties. Vessel dilator (VD), which is located in the same part of the hormone as NP73-102, also prevents lung damage in mice from an allergic asthma attack. VD's mechanism of action is unknown, but we are actively studying it. These therapeutic peptides have a great advantage over conventional drugs. They can be targeted to specific cells by using nanoparticle carriers and produced on location from DNA plasmids encoding the peptides. This increases their pharmacological effectiveness and reduces side effects.

1c. Mutations in the ANP pathway are associated with asthma.

As mentioned before, ANP is a hormone that wears several hats. It was first discovered as the hormone responsible for maintaining sodium-potassium balance in the body and normal blood pressure through regulating the volume of fluid in the blood. Our lab and others, however, have been studying its role in the immune system and have discovered that ANP signaling, through its receptor NPRA, has a major effect on inflammation in asthma, cancer and other diseases. As in all diseases, there is a genetic component along with the effects of environment. We have been studying ANP to determine if mutations in the gene affect its activity. Such changes are known to affect the activity of ANP in regulating blood pressure and cardiovascular disease but few studies have been done to look at the inflammatory aspects of ANP-NPRA signaling. Our results will be published soon and will show that single base changes in the ANP gene can have significant effects on its activity. This knowledge enables us to design better drugs and DNA-based therapeutics to modify the inflammatory activity of ANP in an effort to protect people from diseases such as asthma and allergy.

2. Use of stem cells for reducing inflammation in an experimental asthma model.

The testing of adult stem cells for cell therapy in a variety of human diseases is a rapidly growing area of research. Human bone marrow transplants have been used to cure disease for decades and is an excellent source of adult stem cells. As a model for human experiments, we use stem cells obtained from the bone marrow of mice. Stem cells from healthy mice are grown in culture dishes and then injected into asthmatic mice. The stem cells migrate to the lungs of the asthmatic mice and help to reduce the inflammation and breathing problems that are associated with this disease. The lymphocytes in the asthmatic lung have cytokine profiles that are known as Th2-type. In mice, given intravenous injections of stem cells, the Th2 cells switch to the healthy Th1 type. This new therapy has not been tested on humans but it has a great potential for treating a variety of inflammatory diseases from asthma to lung cancer.

3. The role of microRNAs in the genesis of asthma.

MicroRNAs (miRNAs) are small ribonucleic acid molecules, 18 to 25 bases long, that have a large effect on gene expression. It is estimated that from 30 to 50% of human genes are regulated by miRNAs and one miRNA can control as many as 200 genes. Mutations in the DNA that codes for miRNAs may contribute to many human diseases such as cancer, asthma, allergy and chronic infections. We have developed a microarray detection system for miRNAs that allow us to obtain a profile on the types and amounts of a large number of miRNAs from a person's blood sample. Experiments to correlate miRNA expression with inflammation, allergy, and asthma in a mouse model are being performed as a preliminary to testing miRNA targeting in humans. We are also creating transgenic mouse models that over express or are deficient in these miRNAs in order to study their function.

4. Isolation and characterization of a new human mast cell line (USF-1) as a model for inflammatory disease research.

A stable human mast cell line derived from human cord blood stem cells has been established. Compared to the standard NIH mast cell lines, HMC-1 and LAD-2, this line shows greater stability with respect to the markers FeR1 and CD117, grows faster and requires a much simpler growth medium; hence, it is significantly less expensive to use. USF-1 is not a tumor cell line like the other cell lines, so retains all of its natural physiological functions. Currently we are incorporating the SV40 large T gene into USF-1 to immortalize it. One interesting preliminary result involves the plant compound, resveratrol, which is the active anti-inflammatory principle in grape skins and red wine. Resveratrol has been tested on the new human mast cell line, USF-1. It was found to cause increased production of an anti-inflammatory protein, SirT-1, and to inhibit degranulation and release of histamine from the cells.

B. Biology of host-virus interactions: DNA-based antiviral therapeutics.

1b. Respiratory syncytial virus (RSV) subverts the innate antiviral immune response.

Respiratory syncytial virus kills a substantial number of infants each year and has been associated with pneumonia in the elderly. Vaccination against this virus is largely unsuccessful because RSV is able to inhibit the immune system's antiviral surveillance program. The first protein made by the virus after it infects a cell is called NS1 (nonstructural protein 1). This protein inhibits the activity of interferon which is an antiviral compound critical for the body to mount an effective antiviral defense. Great progress has been made in understanding how NS1 does this and how to counteract the viral subversion of the immune system. These research findings may be extremely beneficial in preventing death and severe illness in babies and young children.

The mitochondria of the cells are targets of the NS1 protein. Mitochondria are primarily known as the producers of ATP, the cell's energy supply, but they also are involved in antiviral defense. Two mitochondrial proteins, MAVS (mitochondrial antiviral signaling gene) and the adaptor protein, RIG-I, have to get together to trigger expression of antiviral genes and it is here that RSV's tactical weapon, NS1, acts. Using a combination of *in vitro* and *in vivo* experiments, we showed that NS1 blocks interaction of MAVS with Rig-I, thereby short-circuiting the antiviral system and prolonging survival of the virus. By preventing the virus from making NS1, we hope to stop RSV infections before they start.

2b. Respiratory syncytial virus NS1 protein is localized to the nucleus.

The activity of the RSV protein, NS1, is quite complex. RSV infects lung cells and makes copies of itself, eventually resulting in damage to the lung that can be lethal. The NS1 protein blocks the antiviral interferon response of the cells allowing the virus to grow. How does NS1 do this? As described above, one way is by interfering with the interaction of mitochondrial proteins; however, NS1 does other things. Data shows that NS1 localizes to the cell's nucleus but in doing so, blocks the entry of a protein called STAT-1 that is necessary for expression of antiviral genes. NS1 binds preferentially to *importin-α5*, a nuclear transport protein, and keeps it from binding to STAT-1. Hence, STAT-1 is prevented from entering the nucleus and cannot switch on the antiviral program. Antiviral therapeutics that block production of NS1 should be effective in restoring a good immune response.

C. Nanomedicine—application of nanotechnology for detection and treatment of human disease.

1c. Microfluidic-microelectronic devices for rapid detection of biomarkers for lung disease.

A microfluidic device using a gold nanowire detector for rapid and sensitive measurement of an inflammatory marker called 8-isoprostane has been developed. The ability to measure this compound in a doctor's office would be highly useful in determining the severity of an asthmatic attack and in testing the effects of combinations of anti-asthmatic drugs. The device has also been successfully modified to measure nitric oxide, another indicator of inflammation associated with asthma. The detector is so sensitive that it can even measure the very low levels of these compounds present in the exhaled breath of a patient. This is a major advance since it does not require taking a blood sample and sending it to a lab for testing.

In principle, the detector could be adapted for the simultaneous detection of many different molecules and also to identify various pathogens such as paramyxovirus and HIV. The military use of these devices under field or battle conditions would provide a great advantage, for example, in screening blood donors for pathogens such as HIV and hepatitis. Such a device is not yet available, but we are working on it.

2c. Development of implantable polymer scaffolds for proliferation of adult human stem cells.

The therapeutic use of adult stem cells will be a major force in medicine in the next decade. There are natural sources of these cells but increased use will quickly outstrip the supply unless methods are found to increase their proliferation under artificial conditions that mimic the body. We have engineered and constructed a spin-coater device that is able to create an artificial scaffold for the growth of stem cells. The material from which the scaffold is generated can be modified chemically in a variety of ways to aid the growth and stability of cells that are attached to the scaffold. Different scaffolds and modifications are being tested to determine which ones give the best growth and maintenance of 'stemness' of the cells. Ultimately, the scaffolds will be implanted into test animals to see how well they can function *in vivo*.

3d. Use of Sertoli cells for targeted delivery of plasmid DNA to lung.

Sertoli cells are found in the testes where they are responsible for nurturing spermatogonial cells and maintaining the proper environment for sperm production. If Sertoli cells are carefully separated from the testes tissue of immature mice, they can be obtained as a relatively pure population with very special properties. We injected Sertoli cells intravenously into mice and found that the cells preferentially ended up in the lung. This specific homing to the lungs makes Sertoli cells a potentially useful candidate for delivery of DNA therapeutics (plasmids) to the lung for treatment of asthma and other lung diseases. Sertoli cells can also be loaded with nanoparticles containing an anti-inflammatory compound such as curcumin. When the cells are injected intravenously, they quickly reach the lung where they break up in the capillary bed and release the nanoparticle cargo.

D. Plant Extracts and Allergic Diseases

1. Curcumin alters dendritic cell activity and reduces inflammation.

Plant extracts and other natural compounds offer a huge area for discovery of novel anti-inflammatory agents. A study of the activity of curcumin, an ingredient in curry powder, was completed this year with extremely interesting findings. Curcumin, which is isolated from the turmeric plant, has been used for years as an alternative medicinal compound in the treatment of a wide variety of inflammatory diseases. We have discovered a link between the anti-inflammatory properties of curcumin and the innate immune system. Dendritic cells are the cells of the immune system that look for pathogens, cancer cells and foreign substances, digest them and 'present' them to the T lymphocytes which then mount an immune response. Our results showed that incubation of dendritic cells with curcumin caused them to undergo changes that reduced their inflammatory activity. While this may sound contrary to what was aforementioned, they sometimes go overboard and cause more damage through excessive inflammatory response. An example of excessive inflammatory response is asthma and severe allergies. It is this over-reaction that curcumin is inhibiting.

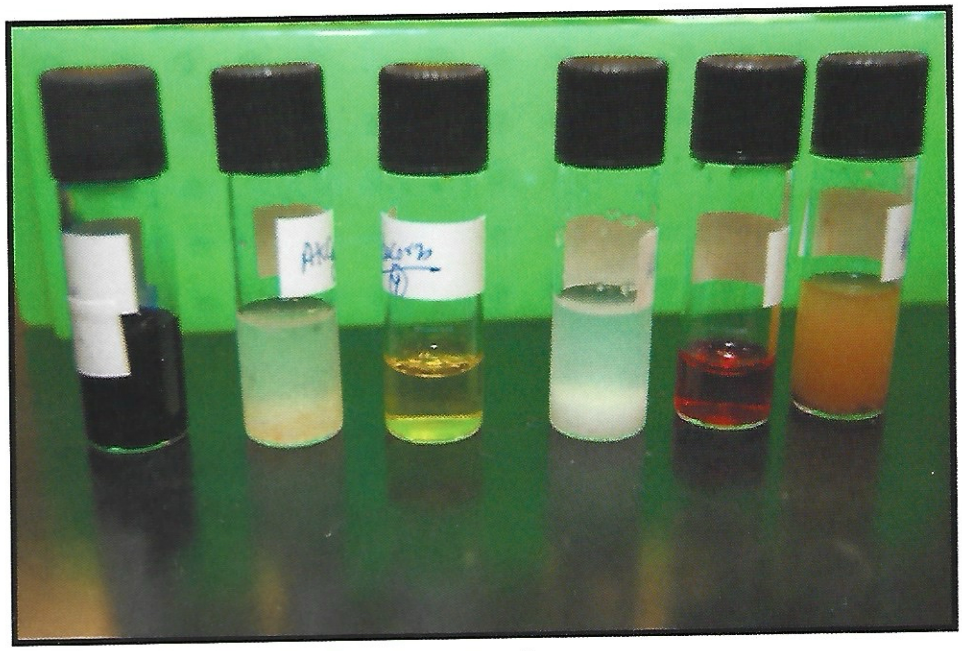
E . Inhibition of tumor cell proliferation

1. NP73-102 inhibits tumor cell proliferation in cell cultures and in animals.

Evidence for the anticancer activity of NP73-102 continues to mount. The combination of a plasmid that produces the peptide with nanoparticles made of the natural polymer chitosan produces a powerful anticancer agent that can be delivered by a variety of routes. We have given it to mice as nose drops, by injection and even as a cream applied to the skin. All of these methods provided significant protection against breast cancer, lung cancer, melanoma, prostate and other tumors. As a further advancement of the study, we are testing NP73-102 against ovarian cancer in rhesus macaques. The results from this study should be available by the end of 2009.

F. Test of anti-HIV microbicides in a non-human primate model

HIV continues to be a serious threat to the health of millions of people worldwide. The spread of the disease by sexual contact could be prevented by the appropriate use of antiviral formulations. We have developed an anti-HIV cream that can be applied intravaginally and it is being tested in a primate model using SHIV, the primate version of the immunodeficiency virus. Safety tests showed that the formulation caused no adverse reactions and we are hopeful that expression of the antiviral agents will prevent the virus from getting a foothold in the vaginal tissue. Positive results in the primate model will allow us to apply for FDA approval of the antiviral formulation.



Nanoparticles

Research Success Possible Through Generous Bequest

The remarkable research success of
Dr. Shyam Mohapatra,
Professor of Medicine
and Director of Basic Research
for Allergy and Immunology at USF Health
and
James A. Haley Veteran's Hospital,
is undeniable proof that planned giving can lead to very big things- even in a field like Nanotechnology.

A nanobiotechnologist, Dr. Mohapatra holds the Mabel and Ellsworth Simmons Endowed Professorship in Allergy and Immunology. The professorship is funded in perpetuity through a bequest from the Simmons estate. "This important endowment set the direction for my research into airway diseases like asthma," Dr. Mohapatra says. "The endowment serves as pilot funding for the exploratory phase of my research so that by the time I'm ready to apply for a grant from the National Institutes of Health, a significant portion of the work will have already been completed." The Simmons endowment continues to set the stage for greater advances in the battle against pulmonary diseases. Dr. Mohapatra is working to develop a new generation of drugs to ultimately replace nebulizers. Nebulizers only deliver 10 percent to 20 percent of a particular medication to the targeted areas, with the rest being lost in the process.

Dr. Mohapatra is advancing technology that will flip these percentages, leading to more effective treatments with fewer side effects. "It's difficult to get external funding to do research until you can prove you're on the right track," he says. "With our endowment funding, we can develop processes and show results quickly, leading to greater funding in the very near future."

CLINICAL RESEARCH PROJECTS

1. Repeated nasal challenge in skin prick-puncture negative, intradermal positive dust mite allergic rhinitis patients

Skin prick-puncture testing is a specific test to determine whether or not an individual is allergic. The primary goal of this study is to evaluate the clinical usefulness of intradermal skin testing when prick-puncture tests are negative. Intradermal skin testing is more sensitive but less specific than prick-puncture testing. There is little evidence-based data to support the clinical relevance of a negative prick-puncture test with a positive intradermal test result. This study's hypothesis is that subjects who have a clinical history of perennial rhinitis symptoms associated with dust exposure or not associated with other perennial allergens, will have a positive challenge with *Dermatophagoides pteronyssinus* when they have a positive interdermal test and a negative prick-puncture test. Subjects who are prick-puncture negative and intradermal skin test positive to *Dermatophagoides pteronyssinus* will be challenged with nasal sprays containing either placebo or *Dermatophagoides pteronyssinus* extract solutions three times daily each for two weeks to determine whether such challenges cause allergic symptoms. Six subjects have screened, 2 subjects have randomized and one subject has completed this study.

2. Pollen and Mold Counts and Immunochemical Quantification of Outdoor Allergens

Particles, other than pollen, which transport aeroallergens, have been described. The Division, which houses the Pollen and Mold Counting Station for Tampa, has two collectors adapted to collect both pollen and pollen aeroallergens. The collectors are located on the roof of the James A. Haley V.A. Medical Center Research Building. Pollen counts are performed twice weekly, disseminated to local media once weekly, and to the Internet twice weekly. Dr. Mary Jelks reads and interprets the slides.

3. Effect of Supplemental Oral Curcumin in Patients with Atopic Asthma

Curcumin, a naturally occurring polyphenolic molecule derived from the root of the *Curcuma Ionga* plant, has been shown in animal models to have intracellular molecular targets such as transcription factors AP-1 and NF-κβ. It prevents the secretion of both pro-inflammatory (TNF-α, IL-6) and anti-inflammatory (IL-10) cytokines. Cucrumin given in vitro to *Dermatophagoides farinae* stimulated lymphocyte cell cultures demonstrated a decreased production of IL-2, IL-4, IL-5, and GM-CSF. The propose of this pilot study is to evaluate the effect of oral supplementation of curcumin on patients with persistent atopic asthma in a randomized, double-blinded, placebo-controlled fashion. Twenty nine subjects have screened for this subject, 17 have randomized and 10 have completed this study.

4. Measurement of natriuretic hormone peptides in exacerbation of asthma

Evidence exists that atrial natriuretic peptide is a regulator of smooth muscle airway tone. In animal models, atrial natriuretic peptide is a potent bronchodilator. Natriuretic hormone peptides include atrial natriuretic peptide, vessel dilator peptide, kalliuretic peptide, long natriuretic peptide and brain natriuretic peptide. For these reasons, we wish to measure atrial natriuretic peptide and 4 other natriuretic hormone peptides (vessel dilator peptide, kalliuretic peptide, long natriuretic peptide and brain natriuretic peptide) encoded by the same gene and derived from the same pro-hormone. We hypothesize that there is a statistically significant decrease of natriuretic hormone peptides in subjects with asthma exacerbation compared to levels following treatment of an exacerbation of asthma. Measurement of natriuretic hormone peptides in a patient suffering an asthma exacerbation may be useful to the clinician. If our hypothesis is correct, and natriuretic hormone peptides are decreased, such information may be valuable to evaluate patients with an exacerbation of asthma. Although asthma presents with shortness of breath, coughing and wheezing, other conditions can also present similarly (congestive heart failure, myocardial infarctions, vocal cord dysfunction, interstitial lung diseases). Studying the relationship of natriuretic hormone peptides during exacerbations may help to better understand the physiology and pathogenesis of asthma. Since the study began, 14 subjects have screened and 10 have completed the study.

5. Procalcitonin as a diagnostic aid in the diagnosis of acute bacterial sinusitis

The purpose of this pilot study is to determine if clinical bacterial sinusitis is associated with elevated procalcitonin. Sinus infection is one of the most commonly diagnosed diseases in the United States, affecting nearly 16% of the population annually. Although viral upper respiratory infection is relatively straightforward in terms of diagnosis and management, the diagnosis of acute bacterial sinusitis is difficult and is often incorrectly made, resulting in a high rate of inappropriate use of antibiotic therapy for viral infections. Current recommendations advise that acute bacterial sinusitis should be suspected when upper respiratory infection symptoms last greater than 10-14 days. Procalcitonin is a 116 amino acid peptide that is a precursor of calcitonin. Although confined mainly to the thyroid C-cells in health, procalcitonin can be induced in multiple cells lines in inflammatory conditions and is elevated in bacterial infections. Procalcitonin levels have been shown to be elevated in bacterial but not in viral infections. We hypothesis that elevated procalcitonin levels predicts the presence of bacterial sinusitis in patients presenting with sinus complaints.

6. Systemic Reactions to Allergen Immunotherapy

The goal of the study is to identify the risk of systemic reactions, predisposing factors and the response to epinephrine given when the first sign of a systemic reaction or anaphylaxis occurs. Allergen immunotherapy is a commonly used therapy for atopic diseases, predominantly allergic rhinitis. It has proved to be effective in reducing the symptoms of allergic rhinitis and asthma. Despite its clinical benefit, there is risk of systemic reactions associated with this procedure. Several studies have evaluated the risk retrospectively, but many limited the definition of systemic reaction. It is suspected that the systemic reaction rate to allergen immunotherapy with aeroallergens is higher than previously reported. This study is a retrospective review of patients with systemic reactions to allergen immunotherapy over a 1-year period. The reactions of patients who report any systemic symptoms (rhinitis, shortness of breath, wheezing, rash, chest tightness, headache, dizziness, light-headedness, abdominal pain, or difficulty swallowing) are recorded at the time of the reaction. Subsequently, charts are reviewed to identify patients at greater risk for a systemic reaction.

7. Efficacy of Using Oxymetazoline Hydrochloride Combined with Nasal Glucocorticosteroid to Treat Perennial Allergic and Nonallergic Rhinitis in Subjects with Persistent Nasal Congestion.

This study hypothesizes that treatment with oxymetazoline, in addition to a nasal glucocorticosteroid for fourteen days, will decrease the nasal congestion persisting in subjects with allergic or nonallergic rhinitis despite maximum recommended dosages of a nasal glucocorticosteroid. It is also hypothesized that nasal glucocorticosteroid therapy will prevent the development of rhinitis medicamentosa secondary to therapy with oxymetazoline. The primary endpoint will be the change in Average Daily Nasal Congestion Scores from baseline to the end of treatment with oxymetazoline. The secondary endpoint will compare quality of life scores at the baseline visit to visits on day 7, day 14, and day 28. Since the study began, 44 subjects have been screened and 26 subjects have been randomized. Subject recruitment is still in progress.

Pending Clinical Research Projects

1. Effects of Pine Cone Extract (PCE) on IgE levels in Patients with Allergic Rhinitis

Pine cones and their aqueous extracts have been known to have medicinal properties in Japanese populations as far back as 2000 years ago. Anecdotal reports have suggested that use of PCE improves allergic rhinitis symptoms and in the mouse model has been shown to significantly reduce serum IgE levels. The purpose of this study will be to determine if oral PCE extract administered in a double blind fashion will significantly reduce IgE levels in patients with evidence of perennial allergies.

2. The Effect of Pine Cone Extract (PCE) on Ova Sensitized Mice

Pine cone extract has been previously shown to reduce levels of IgE and Th2 cytokines including IL-4 as well as enhance production of IFN-gamma and IL-12 in C57BL/6 and Balb/c mice. The purpose of this study will be to analyze the effect of PCE on Th2 cytokines and IgE levels in Balb/cJ mice that have undergone sensitization to ovalbumin.

3. To Determine the Prevalence of Food Allergy in Adult Patients with Eosinophilic Esophagitis

Food allergies are known to play a significant role in children with eosinophilic esophagitis. Little is known about the prevalence of food allergies in adult patients with eosinophilic esophagitis. The purpose of this study will be to determine the prevalence of food allergies in a cohort of adult patients with eosinophilic esophagitis. These results will be compared to findings in adult patients with other swallowing disorders.

4. The Effect of Recurrent Intermittent Hypoxia (IH) Similar to Obstructive Sleep Apnea Syndrome (OSAS) on Airway Hyperesponsiveness and Airway Inflammation in a Mouse Model: The Role of Mast Cells

Several indirect mechanisms have been suggested to lead to asthma worsening in patients with OSAS. To date, evidence of direct correlation between OSAS and asthma is weak, and few studies have been examined in relationship to hypoxia stimulates Hypoxia Induced Fever (HIF) transcription, which in turn increases Vascular Endothelial Growth Factor (VEGF) expression. To our knowledge , no study has been done yet to evaluate the effect of recurrent IH similar to OSAS on HIF-VEGF pathway in mast cells and the consequences in airway and hyperresponsiveness and inflammation. The aim of this study is to clarify mast cell behavior under recurrent IH and to investigate the role of HIF-VEGF pathway of mast cell in worsening coexisting airway hyperresponsiveness and inflammation. The primary endpoints for this study is to compare the airway hyperresponsiveness in recurrent IH exposure mice group to control group. The secondary endpoints are to compare airway inflammation, HIF 1, VEGF, IL-4, IL-5 and IL -13 levels in lung tissue and in bronchoalveolar lavage fluids in mice under IH and after treatment and HIF1 antibodies.

PHARMACEUTICAL SPONSORED STUDIES

Studies funded by pharmaceutical companies are conducted at the Division's Clinical Research Unit (CRU). Funds from these studies support the Division's research and clinical training program. Eight studies were completed in 2008, twelve in 2009 and nine additional studies will continue into 2010. To date, the CRU has agreements for five new studies in 2010.

The CRU is a member of the American Lung Association's Asthma Clinical Research Center network, one of 20 centers throughout the United States. The American Lung Association Clinical Research Center completed two studies in 2008, and one in 2009, three are still in progress. The American Lung Association has several new protocols pending approval.

2008 – 2009 Pharmaceutical Sponsors

Alcon Laboratories
Almirall Pharmaceuticals
Altana/Byk Gulden
AstraZeneca Pharmaceuticals
Dyax Corporation
Forest Laboratories
Genentech Inc.
GlaxoSmithKline
Jerini, US
Merck and Co., Inc.
MedImmune
Novartis Pharmaceuticals
Pharming Inc.
Sanofi-Aventis Pharmaceuticals
Schering-Plough Corporation
Sepracor Inc.
Skye Pharma

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Clinical Research Unit

The University of South Florida, Asthma, Allergy and Immunology Clinical Research Unit was established in 1977 to improve the treatment of patients who suffer from asthma, allergic and immunologic diseases. The Clinical Research Unit is a segment of the Division of Allergy and Immunology, Department of Internal Medicine at the University of South Florida College of Medicine. The Division is affiliated with the H. Lee Moffitt Cancer Center, James A. Haley Veterans Administration Hospital and the University of South Florida Medical Clinics in Tampa. The Unit is also affiliated with All Children's Hospital and Bay Pines Veterans Hospital, both in St. Petersburg.

The Unit provides quality research in a variety of clinical areas which include the following: allergic conjunctivitis; allergen immunotherapy; allergen skin testing; allergic rhinitis; asthma; atopic eczema; bronchitis, acute and chronic; contact dermatitis; chronic obstructive pulmonary disease; exercise induced asthma; headache (migraine and tension); HIV disease and any of its complications; immunodeficiency diseases; insect allergy; intravenous immunoglobulin; osteoporosis; rheumatoid arthritis; sinusitis, acute and chronic; temporomandibular joint disease; urticaria and vasomotor rhinitis.

Clinical Research Unit staff from left to right:

Sarah Lewis, Regulatory Coordinator, Diana Miller, Research Coordinator, Shirley McCullough, Research Coordinator, Michelle Singleton, Clinical Research Administrator

Basic and Clinical Research Support

Endowments

The Joy McCann Culverhouse Endowment

The Mabel and Ellsworth Simmons Endowment

Extramural Funding

American Lung Association
- Asthma Clinical Research Center Award

Florida Biomedical Research

National Institute of Health

National Heart, Lung and Blood Institute

Pfizer Visiting Professor Grant

Veteran Affairs Merit Review Award

Veterans Affairs Career Scientist Award

Florida Hi Tech Corridor Grant

Office of Naval Research Awards

TransGenex Nanobiotech Inc

Division's On-Line Journal

Shyam Mohapatra, Ph.D., Gary Hellermann Ph.D., and staff established an on-line journal, *Genetic Vaccines and Therapy* in 2004 - present. http://www.gvt-journal.com

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ABSTRACTS

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Wang J, Zhang W, Li K, Chen D, Liu G, Lockey RF, Mohapatra SS. Npr1 Deficiency Upregulates Regulatory T Cells (Tregs) Through Impaired Dendritic Cell (DC) Development. 65th Annual American Academy of Allergy, Asthma & Immunology Meeting, Washington, DC, March 13 – 17, 2009. *J Allergy Clin Immunol* 2009; 123(2): S93. (#350).

Wang X, Xu W, Chen D, Kong X, Lockey RF, Mohapatra SS. Modulation of Lung Inflammation by Vessel Dilator, an N-Terminal Natriuretic Peptide, in a Mouse Model of Allergic Asthma. 64th Annual American Academy of Allergy, Asthma & Immunology Meeting, Philadelphia, PA, March 14 – 18, 2008. *J Allergy Clin Immunol* 2008; 121(2): S63. (#243).

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Faculty and Staff Awards: 2008-2009

Roger W. Fox, M.D., Selected as one of *"The Best Doctors in America"* Guide 2008-2009.

Roger W. Fox, M.D., 30 years Department of Veterans Affairs Service Award, 2009.

Mark C. Glaum, M.D., Ph.D., Fellow of the Academy of Allergy, Asthma and Immunology, 2008.

Mark C. Glaum, M.D., Ph.D., Selected as one of *"The Best Doctors in America"* Guide 2008-2009.

Dennis K. Ledford, M.D., Selected as one of *"The Best Doctors in America"* Guide 2008- 2009.

Richard F. Lockey, M.D., Recipient, 2008 AAAAI Distinguished Clinician Award, American Academy of Allergy Asthma and Immunology, March 17, 2008.

Richard F. Lockey, M.D., Florida Super Doctors 2009, special advertising supplement to the Tampa Tribune, Gulf Coast Edition, January 17, 2009.

Richard F. Lockey, M.D., Selected as one of *"The Best Doctors in America"* Guide 2008- 2009.

Shyam S. Mohapatra, Ph.D., Excellence in Innovation Award, University of South Florida, November 7, 2008.

Shyam S. Mohapatra, Ph.D., "International Business Person of the Year" Award by the Indo-US Chamber of Commerce of Tampa Bay, Tampa, 2008.

Shyam S. Mohapatra, Ph.D., Senior VA Career Scientist Award 2008.

J. W. Wang, Ph.D., First Place Allergy Presentation Award, SIPAIID 2nd Annual Symposium 2008.

J. W. Wang, Ph.D., Outstanding poster award, USF Research Day 2008.

Wayne Anderson, Ph.D., Head, Applied Genetics, Respiratory GlaxoSmithKline, Research Triangle Park, North Carolina. "The Double Helix: Changing the Paradigm of Personalized Medicine", September 17, 2008.

Eugene R. Bleecker, M.D., Co-Director, Center for Human Genomics Section Head, Pulmonary, Critical Care, Allergy & Immunologic Diseases, Wake Forest University School of Medicine, Winston-Salem, North Carolina. "Pharmacogenetics and Personalized Medicine in Asthma", August 06, 2008.

Markus W. Ollert, M.D., Professor of Molecular Dermatology & Immunology, Director of Clinical Research Division in Molecular & Clinical Allergotoxicology Vice-Chairman, Dept of Dermatology & Allergy Munich, University of Technology Munich, Germany. "Immunotherapy for Insect Venom Anaphylaxis: from Extracts to Molecules", May 1, 2008.

Gene L. Colice, M.D., Professor of Medicine, The George Washington University School of Medicine, Director, Pulmonary, Critical Care & Respiratory Services Washington Hospital Center, Washington, D.C.. "Inflammation in Small Airways", January 31, 2008.

Newman L. Stephens, M.D., FRCP (London), Professor of Physiology, University of Manitoba, Winnipeg, Canada. " Proliferation (focus on non-muscle myosin light chain kinase) Differentiation (regulation by TGFb1) in smooth muscle", December 4, 2008.

Donald D. Stevenson, M.D., Senior Consultant, Division of Allergy, Asthma & Immunology Scripps Clinic, La Jolla, California. "Aspirin Desensitization"; "Pathogeneses of aspirin exacerbated respiratory disease and reactions to NSAIDs"; "NSAID induced hives and angioedema", June 24-25, 2009.

Michael N. Teng, Ph.D., Assistant Professor, Department of Biochemistry and Molecular Biology, Penn State University. "Multiple Functions of the Human Respiratory Syncytial Virus Nonstructural Proteins in Viral Pathogenesis", June 22, 2009. "Multiple Functions of the Human Respiratory Syncytial Virus Nonstructural Proteins in Viral Pathogenesis"; August 18, 2009.

Mandip Singh Sachdeva, Ph.D., Professor and Section Leader Pharmaceutics, Florida A & M University College of Pharmacy, Editor-in-Chief CRC Critical Reviews in Therapeutic Drug Carrier Systems. "Formulation Approaches to Treat Lung Cancer", June 29, 2009.

Ken Linsky, Pharm.D., Sr. Regional Medical Scientist, Respiratory GlaxoSmithKline. "GlaxoSmithKline Respiratory Sponsored and Supported Research Update and Opportunities", July 16, 2009.

Sailen Barik, Ph.D., Department of Biochemistry and Molecular Biology, University of South Alabama College of Medicine. "Viral counter-attack on cellular RNA interference: A novel mechanism targeting Argonaute", August 13, 2009.

Tom Taylor-Clark, Ph.D., Johns Hopkins University. "The role of the ion channel TRPA1 in the activation of airway sensory nerves by oxidative stress", July 23, 2009.

Narasaiah Kolliputi, Ph.D., Massachusetts General Hospital. "Exogenous Administration of SOCS-1 by gene transfer provides protection against hyperoxia-induced lung injury", September 4, 2009.

Anthony Register, Pharm.D., Sr. Regional Medical Scientist-Respiratory/G.I., Clinical Development and Medical Affairs N.A., GlaxoSmithKline, Inc.. "Use of Advair in Asthma" and "Veramyst for Allergic Rhinitis", September 23-24, 2009.

Rosa Codina, Ph.D., Senior Scientist Greer Laboratories. "An overview of a few miscellaneous topics for discussion, part I", November 12, 2009.

Divisions of Allergy and Immunology Annual Retreat
Hillsborough River State Park
January 16, 2010

From left to right:

Woei Eng, M.D., Monroe J. King, D.O., John Sleasman, M.D., Mandel Sher, M.D., Hugh Windom, M.D., Weidong Zhang, Ph.D., Robert Pesek, M.D., Richard Lockey, M.D., Peggy Hales, Morna Dorsey, M.D., Dennis Ledford, M.D., Elena Perez, M.D., Arun Kumar, Ph.D., Mark Glaum, M.D., Ph.D., Roger Fox, M.D., Michelle Singleton, Dona Shearer, Glenn Whelan, Pharm.D.

Core faculty members not pictured:
Shyam S. Mohapatra, Ph.D., Homero San-Juan-Vergara, M.D., Ph.D., Narasaiah Kolliputi, Ph.D., Srinivas Nagaraj, Ph.D, Michael Teng, Ph.D.

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